ENCLOSURE C

1.132 declaration of Dr. Bradley Galer

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION UNDER 37 C.F.R. 1.132 Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	CALD-007
	First Named Inventor	Caldwell, Larry
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	Application Number	10/029,407
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	Group Art Unit	1615
	Examiner Name	Ghali, Isis D.
	Title:	Methods and compositions for treating headache pain with topical NSAID compositions

Dear Sir:

I, Bradley Galer, am an inventor of the subject matter claimed in the patent application identified above. A copy of my C.V. which demonstrates that I am qualified to speak on the level of one of skill in the art is already of record in this application.

I hereby declare as follows:

1. I have read the Office Action dated March 30, 2006 that issued in the above referenced case. I have also read Van Engelen (U.S. Patent No. 6,416,772), the reference cited in support of the rejections made by the Office.

2. Van Engelen characterizes the topical analgesic solution disclosed therein as follows:

> solution is effective for the relief of aches and pains associated with, among other things, muscular aches, strains and cramps, arthritis, joint pain, burns, lower back discomfort, bursitis, rheumatism, insect bites, and sports injuries, athlete's foot, shingles, headaches, menstrual cramps, and tennis elbow.

See column 3, lines 56 to 62.

3. As can be seen with reference to the above, Van Engelen teaches that the analgesic solution disclosed is effective for relieving the aches and pains of muscles, joints, cramps, headaches and the like. As such, the pain conditions which Van Engelen targets are conditions arising from peripherally induced musculoskeletal mechanisms or peripheral nerve damage (shingles), and not headaches arising from central nervous system mechanisms, such as migraine, cluster, tension headaches, or indomethacin responsive headaches. This can clearly be seen with reference to the working example set forth in Van Engelen, wherein the headache to be treated was simply associated with head pains and not associated with nausea, vomiting, light/sound sensitivities, and/or eye symptoms that are commonly associated with headache conditions that are caused by an underlying disturbance in the central nervous system.

4. In contrast, headaches such as migraine, cluster, tension headaches, and indomethacin responsive headaches (IRH) are not caused by musculoskeletal or peripheral nerve damage mechanisms, rather they are headaches that are caused by disturbances in the central nervous system. See e.g., Exhibit A, Aurora, "Pathophysiology of Migraine Headache" and Dodick, "Indomethacin-responsive Headache Syndromes." Accordingly, migraine, cluster, tension headache, and IRH conditions are considered unique clinical entities distinct from those conditions of headache pains caused by localized musculoskeletal mechanisms (e.g., muscle contractions). In fact, the International Association for the Study of Pain, the world's foremost medical and scientific pain society characterizes migraine headaches as arising from central nervous system mechanisms, and not the musculoskeletal system. See Exhibit B, Page 77.

5. Therefore, one of skill in the art would understand Van Engelen to be directed solely to the treatment of headaches caused by musculoskeletal disorders and that musculoskeletal disorders do not include headaches arising from central nervous system mechanisms (e.g., headaches such as migraine, cluster, tension headaches, or indomethacin responsive headaches). One of skill in the art would understand that musculoskeletal disorders do not include migraine, cluster, tension headaches or IRH because such headaches arise from a completely different system and are categorized differently by the International Headache Society, IHS, the foremost international headache medical and research group, as well, as evidenced by Exhibit C (http://www.i-h-s.org/).

6. As such, Van Engelen does not teach one of skill in the art anything about the treatment of headache conditions arising from central nervous system mechanisms, such as migraine, cluster, tension headaches and/or IRH.

7. Accordingly, one of skill in the art would **not** have a reasonable expectation of success based on Van Engelen in treating headaches with topical NSAID formulations.

I hereby declare that all statements made herein are of my own knowledge and are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued there from.

Respectfully submitted,

Date: 02 JUNE 2006 By: _____
Bradley Galer

enc:

- Exhibit A- Aurora, "Pathophysiology of Migraine Headache," and Dodick, "Indomethacin-responsive Headache Syndromes."
- Exhibit B- Classification of Chronic Pain, page 77
- Exhibit C (http://www.i-h-s.org/)

EXHIBIT A

Pathophysiology of Migraine Headache

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The underlying mechanism of migraine and pain has been unraveled recently with the advent of neuroimaging. In this article mechanism of migraine aura and the pain of migraine are discussed. In addition, interictal studies demonstrating hyperexcitability in migraine are reviewed.

The exact pathogenesis of migraine remains to be determined. The pendulum for concepts of migraine pathophysiology swung between primary vascular or primary neural mechanisms. Harold G. Wolff [1], a pioneer of the vascular theory of migraine, proposed that the neurologic symptoms of the migraine aura were caused by cerebral vasoconstriction, and the headache by vasodilatation. Lashley's [2] experience of his own visual aura led him to the concept of the spreading cortical depression (SCD) of Leão being the primary cause, thus promulgating the neural theory of migraine [3]. Newer imaging techniques have made it possible to study the very early events of migraine; thus both theories have been reconciled by contemporary proponents of a neurovascular mechanism of the migraine attack.

The neurovascular theory of migraine is described first with evidence from recent neuroimaging studies. Then we discuss the increasing body of evidence for the concept of central neuronal hyperexcitability as a pivotal physiologic disturbance predisposing to migraine [4]. The reasons for increased neuronal excitability may be multifactorial. Most recently, abnormality of calcium channels has been introduced as a potential mechanism of interictal neuronal excitability [5]. Mutant voltage-gated P/Q-type calcium channel genes likely influence presynaptic neurotransmitter release, possibly of excitatory amino acid systems or inhibitory. It could therefore be hypothesized that genetic abnormalities result in a lowered threshold of response to trigger factors. It has also been suggested that it is theoretically possible for all individuals to suffer a migraine attack, because migraine is an episodic disorder involving head pain and cortical phenomena without structural abnormalities. Therefore, only investigations aimed at studying the function of the brain provide an insight into migraine pathophysiology. In this article, the mechanism of aura and head pain are discussed first, followed by a discussion of interictal disturbances, which lead to a propensity to developing migraine.

Mechanisms of Aura

The unpredictable and elusive nature of migraine has prevented many investigators from systematically studying migraine aura. Recent studies by Cao *et al.* [6••], wherein migraine was reliably visually triggered in 50% of subjects, enabled the immediate early events of the migraine attack to be measured for the first time. A red and green checkerboard was used for visual stimulation because migraineurs are known to be sensitive to linear stimuli. Using the recently developed fMRI based on the blood oxygen level-dependent (fMRI-BOLD) technique, the authors were able to measure, with millimeter resolution, second-to-second activation of occipital cortex to visual stimulation in subjects with migraine. None of the six normal controls developed a headache and displayed normal patterns of BOLD signals on visual activation. Six patients with migraine with aura (MwA) and two patients with migraine without aura (MwoA) had experienced visually triggered headache; two also had accompanying visual change. Headache was preceded by suppression of initial activation that slowly propagated into contiguous occipital cortex at a rate ranging from 3 to 6 mm per minute. This neuronal suppression was accompanied by an increase in baseline contrast intensity, indicative of vasodilatation and tissue hyperoxygenation. The baseline contrast increases that indicated tissue hyperoxygenation were similar to those witnessed in experimental SCD [7]. These spreading events accompanied visually triggered headache whether or not it was associated with visual change. In this study patients were selected based on a history of visually triggered headache, so that generalizing these findings to all migraine patients must be done with caution. Nevertheless, previously hypothesized mechanisms of SCD in migraine were clarified by this study, and the previously controversial findings of ischemia accompanying migraine aura were not supported.

In a different study using perfusion-weighted imaging (PWI), another novel functional neuroimaging technique particularly suited to study short-lived events such as migraine aura, 19 patients were studied during spontaneous migraine [8••]. Twenty-eight attacks were studied because some patients were imaged more than once. There was relative reduction of cerebral blood flow in the occipital cortex

contralateral to the visual defect during MwA, but observed only in the occipital cortex and not other brain regions. One subject with attacks of both MwA and MwoA demonstrated these phenomena only during MwA. No significant changes in blood flow were observed in MwoA. The hemodynamic changes were demonstrated only on PWI and not on diffusion-weighted imaging (DWI); DWI is sensitive to ischemia and thus further supports MwA not being an ischemic event.

Although these imaging studies favor the neural basis of migraine, they are not able to demonstrate SCD as the putative mechanism of migraine aura. To date, SCD has been recorded successfully in animal models only [9]. In animals, the SCD's band of hyperexcited neurons travels into the sulci or fissures eliciting a magnetoencephalographic (MEG) signal. Using the seven channels of MEG, Barkley *et al.* [10] reported DC shifts in spontaneous migraine. A further study of a larger number of patients has not been possible because of the unpredictable nature of migraine and time of capture of these spontaneous events. Using the visual trigger modeled by Cao *et al.* [6••], Bowyer *et al.* (Paper presented at the Congress of the International Headache Society, Barcelona, Spain, 1999) have now been able to detect DC shifts when headache or aura was precipitated. These studies were performed using the whole head MEG, which permits precise localization of signals. In this study headache was triggered in five of eight migraine patients and none of the six controls. DC-MEG shifts were observed in migraine subjects during visually triggered aura and in a patient studied during the first few minutes of spontaneous aura. No DC-MEG shifts were seen in control subjects. This is additional evidence supporting the primary neural basis migraine and confirms MEG-recorded DC shifts typical of those found during SCD, reported previously in migraine attacks.

Mechanism of Pain

The brain stem and specifically the trigeminovascular system have been implicated to play a large role during a migraine attack from recent experimental and clinical data [11]. It is hypothesized that a sterile inflammatory response occurs due to the release of neuropeptides, *ie*, calcitonin gene-related peptide, neurokinin A, and substance P [12]. The development of novel antimigraine drugs for the treatment of migraine has been based predominantly on these animal models. This mechanism is further strengthened by the discovery of binding sites for the 5 $HT_{1B/1D}$ agonists on brain stem structures [13,14]. The first human study to show activation in the brain stem used positron emission tomography (PET) performed in subjects during spontaneous migraine. Because PET lacks sufficient resolution for exact anatomic localization, the activation was hypothesized to be in the regions of the dorsal raphe nuclei, periaqueductal gray, and locus caeruleus [15]. Recently, an isolated case report found red nucleus (RN) and substantia nigra (SN) to be activated in a spontaneous migraine attack [16]. The same authors also now report the RN and SN to be activated in the subjects with visually triggered migraine [17].

The RN and SN are best known for their functional roles in motor control. The RN, however, has also been associated with pain and/or nociception. Numerous animal studies have documented a response of RN neurons to a variety of sensory and noxious stimuli. In a PET study performed on normal volunteers during capsaicin-induced pain, ipsilateral activation of RN was documented [18]. It remains to be clarified whether or not the RN is involved in the pain pathways or in the motor response to pain.

Evidence of Interictal Disturbances

Electroencephalography (EEG) was one of the first techniques that was undertaken to discern physiologic differences between migraine and controls. A recent review suggests that EEG is not valuable as a diagnostic tool for primary headache disorders [19]. The enhanced photic drive response on the EEG H-response, which was thought to be characteristic of migraine [20], has recently been confirmed by spectral analysis [21,22]. The specificity of the H-response, however, has been questioned because it may occur with other primary headache disorders [19]. Abnormal steady state response evoked by a sine-wave visual stimulus was seen in migraineurs, and improved after administration of propranolol [23,24]. Finally, following a repetitive pattern-reversal stimulation, migraineurs, but not controls, displayed potentiation of visual-evoked potential (VEP) amplitude, which reached its maximum in the second to fourth blocks [25]. Similar results were seen using prolonged stimulation [26]. More recently, however, and in agreement with VEP studies, strong interictal dependence of the auditory-evoked potentials on stimulus intensity was demonstrated in migraine [27]. Furthermore, the response was modulated by zolmitriptan [28]. Transcranial magnetic stimulation (TMS) has been developed to noninvasively study cortical physiology [29,30], and this technique is now increasingly being used to study migraine.

TMS of Motor Cortex in Migraine

Several studies have investigated the motor cortex of migraineurs using TMS. Three studies have been performed on the motor cortex, two of which reported increased excitability in migraineurs and suggested that this neurophysiologic correlate may have a role in migraine mechanisms [31,32]. The first study compared subjects with migraine with and without aura to controls, who demonstrated an increased motor threshold in classic migraine [31]. The motor threshold was increased on the side corresponding to the aura. The threshold difference could not be attributed to attack frequency. The second study was performed on menstrual migraineurs during the cycle compared with controls [32]. An increased threshold was demonstrated, similar to the first study, but in this study the patients had MwoA.

Following these studies two other studies were performed. In the first study there was a difference in amplitude of motor-evoked potentials in MwA compared to controls, but found no differences in the motor threshold [33]. The differences in this study compared to previous reports of increased threshold were explained on the basis of attack frequency, which was higher in their group of patients.

In a second study performed on familial hemiplegic migraine, the threshold of motor cortex was higher on the side corresponding to the aura [34]. Using paired pulses a recent study demonstrated reduced motor cortical excitability after administration of zolmitriptan, a centrally acting 5 $HT_{1B/1D}$ used in the treatment of migraine [35]. This technique thus provides a new opportunity to study cortical physiology and the effects of drugs in migraine.

Cortical Silent Period in Migraine

Two studies have examined the cortical silent period (CSP). Although the results were judged to be preliminary, both reported no differences in CSP at high levels of stimulus intensity [36,37], but at low stimulus intensity a shorter CSP was documented in MwA compared to controls [37]. Because the CSP, in part, is a measure of central inhibition of motor pathways, this shortening of the CSP suggests reduced central inhibition, inferring increased excitability.

TMS of Occipital Cortex in Migraine

Using TMS to study the occipital cortex is perhaps more relevant to migraine because enhanced excitability of the occipital cortex may underlie either spontaneous or visually triggered migraine aura [4]. Occipital cortex excitability in migraine has been evaluated by the generation of phosphenes by the TMS of occipital cortex. The first study reported a low threshold for a generation of phosphenes in subjects with MwA, inferring hyperexcitability of the occipital cortex [38]. In contrast, occipital cortex hypoexcitability was reported in MwA based on a lower prevalence of phosphenes stimulated by TMS [36]. Important technical differences, such as the type of stimulator or coil size, might explain these conflicting findings [39]. Since these early reports there have been two more studies performed on the occipital cortex using TMS, both confirming the initial reports of hyperexcitability [40,41••]. In one of these, hyperexcitability of the occipital cortex was associated with a propensity to visually triggered headache in the same patients [41••].

Conclusions

We currently conceive of a migraine attack as originating in the brain. Triggers of an attack initiate a depolarizing neuroelectric and metabolic event likened to the SCD of Leão. This event activates the headache and associated features of the attack by mechanisms that remain to be determined, but appear to involve either peripheral trigeminovascular or brain stem pathways, or both. Excitability of cell membranes, perhaps in part genetically determined, is the brain's susceptibility to attacks. Factors that increase or decrease neuronal excitability constitute the threshold for triggering attacks.

Using a model of visual stress–induced migraine or by studying spontaneous attacks, and applying advanced imaging and neurophysiologic methods, results have been obtained that support spreading neuronal inhibition as the basis of aura. This neuroelectric event is accompanied by hyperoxia of the brain, possibly associated with vasodilatation. Evidence has been obtained also that the spreading cortical event can activate subcortical centers possibly involved in nociception and associated symptoms of the migraine attack. Susceptibility to migraine attacks appears related to brain hyperexcitability. These newer techniques of functional neuroimaging have confirmed the primary neural basis of the migraine attack with secondary vascular changes, reconciling previous theories into a neurovascular mechanism.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Wolff HG: *Headache and Other Head Pain*, edn 2. New York: Oxford University Press; 1963.
2. Lashley KS: **Patterns of cerebral integration indicated by the scotomas of migraine.** *Arch Neurol Psychol* 1941, 46:331–339.
3. Leão AAP: **Spreading depression of activity in the cerebral cortex.** *J Neurophysiol* 1944, 8:379–390.
4. Welch KMA, D' Andrea, Tepley N, *et al.*: **The concept of migraine as a state of central neuronal hyperexcitabiliy.** *Neurol Clin* 1990, 8:817–828.
5. Ophoff RA, Terwindt GM, Vergouwe MN, *et al.*: **Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca^{+2} channel gene CACNL1A4.** *Cell* 1996, 87:543–552.
6. •• Cao Y, Welch KMA, Aurora SK, Vikingstad EM: **Functional MRI-BOLD of visually triggered headache and visual change in migraine sufferers.** *Arch Neurol* 1999, 56:548–554.

Headache and visual change were triggered by visual stress, and early events in migraine were studied with BOLD effect functional MRI. Similar changes were seen in both migraine with and without aura.

7. Gardner-Medwin AR, Bruggen NV, Williams SR, Ahier RG: **Magnetic resonance imaging of propagating waves of spreading depression in the anaesthetised rat.** *J Cereb Blood Flow Metab* 1994, 14:7–11.
8. •• Sanchez del Rio M, Bakker D, Wu O, *et al.*: **Perfusion weighted imaging during migraine spontaneous visual aura and headache.** *Cephalalgia* 1999, 19:704–707.

Using PWI, spontaneous attacks of migraine were studied. Some subjects were studied several times. This report confirmed previous findings of perfusion changes but not diffusion changes, which support the theory that migraine is not due to ischemia.

9. Bowyer SM, Okada YC, Papuashvili N, *et al.*: **Analysis of magnetoencephalograhic signals of spreading cortical depression with propagation constrained to a rectangular cortical strip: I. Lissencephalic rabbit model.** *Brain Res* 1999, 843:71–78.
10. Barkley GL, Tepley N, Nagel-Leiby S, *et al.*: **Magnetoencephalograhic studies of migraine.** *Headache* 1990, 30:428–434.

11. Raskin NH, Hosobuchi Y, Lamb S: Headache may arise from perturbation of the brain. *Headache* 1987, 27:416–420.
12. Moskowitz MA: The neurobiology of vascular head pain. *Ann Neurol* 1984, 15:157–168.
13. Goadsby PJ, Gundlach AL: Localization of 3H-dihydroergotamine-binding sites in cat central nervous system: relevance to migraine. *Ann Neurol* 1991, 29:91–94.
14. Longmore J, Shaw D, Smith D, *et al.*: Differential distribution of 5-HT 1D and 5-HT 1B immunoreactivity within the human trigemino-cerebrovascular system: implications for the discovery of new anti-migraine drugs. *Cephalalagia* 1997, 17:835–842.
15. Weiller C, May A, Limmroth V, *et al.*: Brainstem activation in spontaneous human migraine attacks. *Nat Med* 1995, 1:658–660.
16. Welch KMA, Cao Y, Aurora SK, *et al.*: MRI of the occipital cortex, red nucleus, and substantia nigra during visual aura of migraine. *Neurology* 1998, 51:1465–1469.
17. Cao Y, Aurora SK, Vikingstad EM, *et al.*: Functional MRI of the red nucleus and occipital cortex during visual stimulation of subjects with migraine. *Cepahalalgia* 1999, 19:462.
18. Iadarola MJ, Berman KF, Zeffiro TA, *et al.*: Neural activation during acute capsaicin-evoked pain and allodynia assessed with PET. *Brain* 1998, 121:931–947.
19. Gronseth GS, Greenberg MK: The utility of the electroencephalogram in the evaluation of patients presenting with headache: a review of the literature. *Neurology* 1995, 45:1263–1267
20. Golla FL, Winter AL: Analysis of cerebral responses to flicker in patients complaining of episodic headache. *Electroencephalopgr Clin Neurophysiol* 1982, 53:270–276
21. Simon RH, Zimmerman AW, Tasman A, Hale MS: Spectral analysis of photic stimulation in migraine. *Electroencephalogr Clin Neurophysiol* 1982, 53:270–276.
22. Pechadre JC, Gibert J: Demonstration, by the cartographic test, of an unusual reaction to intermittent light stimulation in patients with migraine. *Encephale* 1987, 13:245–247.
23. Nyrke T, Kangasniemi P, Lang AH: Difference of steady-state visual evoked potential in classic and common migraine. *Electroencephalopgr Clin Neurophysiol* 1989, 73:284–294.
24. Nyrke T, Kangasniemi P, Lang AH: Steady-state visual evoked potentials during migraine prophylaxis by propranolol and femoxetine. *Acta Neurol Scand* 1984, 69:9–14.
25. Schoenen J, Wang, W, Albert A, Delwaide PJ: Potentiation instead of habituation characterizes visual evoked potentials in migraine patients between attacks. *Eur J Neurol* 1995, 2:115–122.
26. Afra J, Cecchini AP, DePasqua V, *et al.*: Visual evoked potentials during long periods of pattern-reversal stimulation in migraine. *Brain* 1998, 121 (Pt 2):233–241.
27. Wang W, Timsit-Berthier M, Schoenen J: Intensity dependence of auditory evoked potentials is pronounced in migraine: an indication of cortical potentiation and low serotonergic neurotransmission? *Neurology* 1996, 46:1404–1409.
28. Cecchini AP, Afra J, Schoenen J: Intensity dependence of the cortical auditory evoked potentials as a surrogate marker of central nervous system serotonin transmission in man: demonstration of a central effect for the 5-HT1B/1D agonist zomitriptan (311C90, Zomig). *Cephalalgia* 1997, 17:1–18.
29. Barker AT, Freeston IL, Jalinous R, Jarratt JA: Magnetic stimulation of the human brain and peripheral nervous system: an introduction and the results of an initial clinical evaluation. *Neurosurgery* 1987, 20:100–109.
30. Barker AT, Jalinous R, Freeston IL: Non-invasive magnetic stimulation of human motor cortex. *Lancet* 1985, 1:1106–1107.
31. Maertens de Noordhout AL, Pepin JL, Schoenen J, Delwaide PJ: Percutaneous magnetic stimulation of the motor cortex in migraine. *Electroencephalogr Clin Neurophysiol* 1992, 85:110–115.
32. Bettucci D, Cantello R, Gianelli M, *et al.*: Menstrual migraine without aura: cortical excitability to magnetic stimulation. *Headache* 1992, 32:345–347.
33. van der Kamp W, Maassenvandenbrink A, Ferrari MD, vanDijk JG: Interictal cortical hyperexcitability in migraine patients demonstrated with transcranial magnetic stimulation. *J Neurol Sci* 1996, 139:106–110.
34. van der Kamp W, Maassenvandenbrink A, Ferrari MD, vanDijk JG: Interictal cortical excitability to magnetic stimulation in familial hemiplegic migraine. *Neurology* 1997, 48:1462–1464.
35. Werhahn KJ, Förderreuther S, Straube A: Effects of serotonin 1B/1D receptor agonist zolmitriptan on motor cortical excitability in humans. *Neurology* 1998, 51:896–898.
36. Afra J, Mascia A, Gérard P, *et al.*: Interictal cortical excitability in migraine: a study using transcranial magnetic stimulation of motor and visual cortices. *Ann Neurol* 1998, 44:209–215.
37. Aurora SK, Al-Sayed F, Welch KMA: The cortical silent period is shortened in migraine with aura. *Cephalalgia* 1999, 19:708–712.
38. Aurora SK, Al-Sayed F, Welch KMA: The threshold for magnetophoshenes is lower in migraine. *Neurology* 1999, 52:A472.
39. Aurora SK, Welch KMA: Phosphene generation in migraine [letter]. *Ann Neurol* 1999, 45:416.
40. Aggugia M, Zibetti M, Febbraro A, Mutani R: Transcranial magnetic stimulation in migraine with aura: further evidence of occipital cortex hyperexcitability [abstract]. *Cephalalgia* 1999, 19:465.
41. •• Aurora SK, Cao Y, Bowyer SM, Welch KMA: The occipital cortex is hyperexcitable in migraine; evidence from TMS, fMRI and MEG studies (Wolff Award 1999). *Headache* 1999, 39:469–476.

Includes the study of patients with three noninvasive techniques. The patients were found to have hyperexcitability in the interictal period and a greater propensity to visually triggered migraine.

Indomethacin-responsive Headache Syndromes

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Indomethacin-responsive headache syndromes represent a unique group of primary headache disorders characterized by a prompt and often complete response to indomethacin to the exclusion of other nonsteroidal anti-inflammatory drugs and medications usually effective in treating other primary headache disorders. Because these headache disorders can easily be overlooked in clinical practice, they likely are more common than previously recognized. Indomethacin-responsive headache syndromes can be divided into several distinct categories: a select group of trigeminal-autonomic cephalgias, valsalva-induced headaches, and primary stabbing headache (ice-pick headache or jabs and jolts syndrome). Each category can be differentiated clinically and by the extent to which the individual headache disorders respond to indomethacin. The paroxysmal and continuous hemicranias invariably respond in an absolute manner to indomethacin, whereas valsalva-induced and ice-pick headaches may respond in an equally dramatic, but somewhat less consistent fashion. Hypnic headache recently has been described as another primary headache disorder that may respond to indomethacin.

Introduction

The trigeminal-autonomic cephalgias (TACs), a term coined by Goadsby and Lipton [1], represent a group of primary headache syndromes manifested by pain in the somatic distribution of the trigeminal nerve and autonomic signs that reflect activation of the cranial parasympathetic pathways. Despite these shared features, the paroxysmal hemicranias and hemicrania continua (HC) differ from other TACs such as cluster headache and short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) syndrome, primarily with regard to the duration and frequency of attacks and, more germane to this discussion, the response to indomethacin. Valsalva-induced headache disorders also respond to indomethacin, but the response is less consistent. The syndrome of primary stabbing headache is common and usually requires no treatment because the paroxysms of pain last seconds and occur infrequently. However, in rare instances, the pain may occur repetitively over days to weeks and require treatment. In this setting, indomethacin also is effective. The response to indomethacin is not a diagnostic criterion for the diagnosis of valsalva-induced headaches or primary stabbing headache. In contrast, a response to indomethacin is considered by the International Headache Society (IHS) to be an obligatory criterion for the diagnosis of paroxysmal hemicrania or HC.

Etiology and Pathophysiology

The syndromes responsive to indomethacin are primary headache disorders whose etiology remains unknown. As with any headache disorder, when the clinical features are atypical or when abnormal neurologic signs are present, a careful medical and neurologic evaluation is necessary to exclude an organic etiology. Various organic causes, which may mimic the TACs and valsalva-induced headaches, have been described. Therefore, magnetic resonance imaging (MRI) is appropriate in every patient with atypical clinical features and in every patient with cough or valsalva-maneuver headaches to evaluate for cervical-medullary junction abnormalities such as a type-1 chiari malformation.

Trigeminal-autonomic cephalgias

Although the pathophysiology has not been clearly elucidated, the clinical manifestations are thought to reflect activation of the trigeminal and cranial autonomic (parasympathetic) pathways. The central origin of the trigeminal and cranial parasympathetic pathways reside respectively in the caudal trigeminal nucleus and superior salivatory nucleus. The cell bodies in the latter give rise to parasympathetic preganglionic efferents, which travel with the facial (VII) nerve. These fibers pass by way of the geniculate ganglion and ultimately synapse in the sphenopalatine and otic ganglia. Postganglionic fibers travel with the greater superficial petrosal nerve to provide vasomotor innervation to the cerebral blood vessels and secretomotor innervation to the lacrimal glands and nasal mucosa. Activation of the trigeminovascular or parasympathetic pathway can lead to a reflex activation of the other through a functional brain stem connection.

The clinical relevance of this anatomic relationship in human headache conditions is supported by a series of ani-

Table 1. Indomethacin-responsive headache syndromes

Trigeminal-autonomic cephalgias
Paroxysmal hemicranias
Chronic paroxysmal hemicrania
Episodic paroxysmal hemicrania
Hemicrania continua
Valsalva-induced headaches
Primary cough headache
Primary exertional headache
Primary headache associated with sexual activity (preorgasmic and orgasmic)
Primary stabbing headache (jabs and jolts syndrome)
Hypnic headache

mal and human experiments demonstrating local release of trigeminal (calcitonin gene-related peptide) and parasympathetic (vasoactive intestinal polypeptide [VIP]) marker peptides from their respective perivascular nerve fibers after ganglionic stimulation [2]. Both of these peptides are known to be potent vasodilators that may explain the painful vasodilation, which is thought to be responsible, in part, for the head pain. These marker peptides also have been found to be markedly elevated in patients with cluster headache and chronic paroxysmal hemicrania (CPH) during attacks when measured in the ipsilateral external jugular vein [3,4]. Furthermore, after successful treatment with indomethacin, these peptide levels return to baseline values [4]. Although the mechanism by which these pathways are activated is unclear, recent evidence from functional neuroimaging studies in patients with cluster headache and SUNCT syndrome implicates the posterior hypothalamic grey matter [5,6]. This region contains the suprachiasmatic nucleus, the human biologic pacemaker, and may explain the circadian and circannual rhythmic periodicity of these disorders.

Valsalva-maneuver headaches

The pathogenesis of these headaches is unknown. Intuitively, the clinical features of these headaches would seem to imply that a significant but transient increase in intracranial pressure (ICP) may underlie the headache in these patients. Arnold-chiari malformations, subarachnoid hemorrhage, and intracerebral metastases, all of which may raise ICP, have been shown to mimic these headache syndromes [7]. In addition, lumbar puncture has been shown to promptly relieve cough headache for a variable period of time in a small series of patients [8].

Clinical Features

Paroxysmal hemicranias

The paroxysmal hemicranias are characterized by frequent short-lasting unilateral headaches. The female:male ratio is approximately 2:1 and the disorder usually begins in adulthood, with a mean age of 34 years [9]. However, the age of onset is quite variable, ranging from 6 to 81 years. The clinical profile of CPH and episodic paroxysmal hemicrania (EPH) are quite similar, the only difference being the presence of pain-free remissions with the latter. The pain is predominantly in the anterior head region (orbital or temporal) and usually lasts between 2 and 45 minutes. In a recent study, the headaches lasted less than 30 minutes in more than 50% of 78 patients [10]. In a retrospective study of 84 patients, the mean attack duration was 21 minutes and the mean attack frequency was 11 daily (range, 6 to 40) [9]. In a prospective study of 105 attacks, the mean attack duration was 13 minutes (3–46 minutes) and the mean attack frequency was 14 daily (range, 4 to 38) [11]. This is in contrast with cluster headache where less than 6% of headaches last less than 30 minutes and more than 90% of patients have fewer than three attacks daily [12].

The pain is strictly unilateral in most patients, although, in some cases, the pain may alternate sides or, more rarely, occur bilaterally. The pain is described as throbbing, boring, pulsatile, or stabbing that ranges from moderate to excruciatingly severe in intensity. During attacks, one or more ipsilateral autonomic symptom or sign will be present. Lacrimation and nasal congestion are the most common accompanying features and often are quite robust. Conjunctival injection and rhinorrhea also occur in up to one third of patients. Similar to episodic cluster headache, EPH differs from CPH by having attack phases that are interrupted by longer lasting remission phases. The headache phase can last from 2 weeks to 4.5 months; remissions range from 1 to 36 months. Approximately one third of attacks occur during nocturnal sleep in both disorders and attacks have been reported to occur in association with rapid eye movement sleep.

Hemicrania continua

As the name implies, HC is characterized by a headache that is unilateral and continuous. In a review of 34 patients [13], the age of onset ranged from 11 to 58 years (mean, 34 years) and the female:male ratio was 1.8:1. The headaches are strictly unilateral, described as aching or throbbing, and, although moderate in intensity, the continuous background pain is punctuated by severe exacerbations that can last from hours to days. Autonomic features often accompany the headache, especially during exacerbations, but are less prominent than seen with the paroxysmal hemicranias. In addition to cranial autonomic symptoms, migraine-related symptoms occur commonly in this disorder, especially during painful exacerbations. In a recent series of 26 patients, nausea (46%), vomiting (15%), phonophobia (46%), photophobia (54%), and osmophobia (27%) occurred during moderate to severe pain episodes [14••]. Visual aura also has been described in patients with indomethacin-responsive HC [15]. In 75% of patients, ice-pick headache (jabs and jolts) occur during some exacerbations. Despite the term "continua," approximately one third of patients describe an intermittent pattern of headache with bouts of pain lasting weeks to months separated by pain-free remissions [16].

Table 2. Precipitating factors, duration, and location and onset*

	Primary cough headache	Primary exertional headache	Primary headache associated with sexual activity
Precipitating factors	Cough, sneeze	Physical exercise	Sexual excitement
Duration	Less than 1 minute	5 minutes to 24 hours	1 minute to 3 hours
Location and onset	Bilateral and sudden	Bilateral and sudden	Bilateral and sudden

*Each headache type can be prevented by avoiding the activity responsible for precipitating the headache. Primary cough headache may be diagnosed after imaging has excluded a posterior fossa abnormality. Primary exertional headache can be diagnosed after systemic and intracranial causes (subarachnoid hemorrhage, intracranial tumor, sinusitis) have been excluded. Primary headache associated with sexual activity may be diagnosed only after subarachnoid hemorrhage has been excluded.

Valsalva maneuver headaches

Cough headache is defined as transient severe head pain that occurs when coughing, sneezing, weight-lifting, bending, straining at stool, or stooping. Rooke [17] proposed the broader term benign exertional headache for any headache that is precipitated by exertion, has an acute onset, and is not associated with structural central nervous system disease, thus combining cough and exertional headache. The disorder is uncommon. Rooke [17] described 93 cases diagnosed at the Mayo Clinic during a 14-year period, while a recent population-based study revealed a 1% prevalence of benign cough and exertional headache [18]. It is clinically useful to consider these disorders as valsalva-induced headaches because they share a common response to indomethacin. However, the IHS separates benign cough, exertional, and sexual headaches because they have different clinical features and differential diagnoses [19]. The clinical features of these disorders are outlined in Table 2.

For each of these typically benign primary headache disorders, a variety of underlying organic causes can present with an otherwise similar clinical picture. However, there are a number of important features that can help distinguish benign from symptomatic cases and help guide the diagnostic evaluation. A review of 72 benign and symptomatic cases of cough, exertional, and sexual headache demonstrated that symptomatic cough headache began earlier in life (< 50 years), tended to last longer (up to several days vs < 30 minutes), was more frequent than benign cough headache, and did not respond to indomethacin [7]. In a substantial proportion of symptomatic patients, headache may be the only symptom and, despite the posterior fossa location of most of the underlying lesions, the neurologic examination may be normal. A variety of posterior fossa abnormalities have been described in patients with cough headache, but Arnold-chiari type-1 malformations are the most common. Therefore, MRI, which is superior to computed tomography (CT) for the evaluation of posterior fossa and craniocervical junction abnormalities, is recommended in the evaluation of every patient with a new presentation of cough headache.

Symptomatic exertional and sexual headaches begin later in life and last longer than benign exertional and sexual headaches. Symptomatic headaches often are acute in onset, bilateral, very severe, last longer than 24 hours, and may persist for weeks [7]. Because many patients with symptomatic exertional or sexual headaches have subarachnoid hemorrhage as the underlying cause, symptoms or signs of meningeal irritation are invariably present. In addition, patients with subarachnoid hemorrhage had one headache episode only [7]. Therefore, for all new presentations of exertional or sexual headache, appropriate imaging in search of a subarachnoid hemorrhage or intracranial lesion should be obtained. If the CT scan or MRI are normal, a cerebrospinal fluid (CSF) examination should be performed.

Primary stabbing headache

Idiopathic stabbing headache (ISH), commonly known as ice-pick headache, is a common but unusual disorder characterized by ultrashort (1–2 seconds) stabbing pain attacks with a unilateral or bilateral localization varying from one area of the head to another. ISH is a benign primary headache disorder, usually with onset in the middle or late stages of life, with an average age of onset of 47 years. Its main clinical features are brief paroxysms with a unifocal or multifocal location in the head (the pain changing location frequently), marked variability in the frequency of attacks, an irregular or sporadic temporal pattern in most cases, paucity of associated symptoms or signs, coexistence with other headaches (migraine, cluster headache, CPH, and HC) in more than 50% of cases with or without a temporal occurrence of both types of pain, female preponderance, and a partial or complete response to indomethacin [20]. In rare instances, patients may develop repetitive and persistent volleys of attacks, which has been referred to as ice-pick status.

Hypnic headache

Hypnic headache syndrome is a benign, recurrent short-lasting headache disorder that occurs exclusively during sleep and usually after the age of 50 years [21]. The headaches occur at least four nights each week and usually at a consistent time each night [22]. The headaches are moderate in intensity, may be bilateral or unilateral, and are more common in women (3:1). Unlike cluster headache, which also occurs frequently during nocturnal sleep, hypnic headache is not associated with autonomic symptoms such as tearing or rhinorrhea. Uncommonly, nausea, photophobia, and phonophobia may

Table 3. Primary short-lasting headaches

Autonomic features	No autonomic features
Cluster headache	Trigeminal neuralgia
Paroxysmal hemicrania	Primary stabbing headache
SUNCT syndrome	Valsalva-induced headache
Cluster-ic headache	Cough headache
Chronic paroxysmaltic syndrome	Benign exertional headache
Hemicrania continua	Headache associated with sexual activity
	Hypnic headache

Table 4. Paroxysmal hemicrania: differential diagnosis

Feature	Cluster	Chronic paroxysmal hemicrania	Episodic paroxysmal hemicrania	SUNCT	Primary stabbing headache	Trigeminal neuralgia
Gender (male to female)	4 to 1	1 to 3	1 to 1	3 to 1	More women than men	More women than men
Attack duration	1 hour	20 minutes	20 minutes	60 seconds	I second	I second
Attack frequency	One to three	Five to 15	Five to 15	Up to 100 daily	Few to many	Few to many
Autonomic features	Yes	Yes	Yes	Yes	Yes	No
Indomethacin effect	Yes	Yes	Yes	No	No	No

be present. The headaches generally last for less than 60 minutes, although some patients describe some headaches that last up to 6 hours. Patients often find that rising from bed alleviates the pain, whereas lying supine intensifies and may prolong the pain. Lithium is invariably effective [21], but not all patients, especially the elderly, can tolerate the side effects of this medication. Caffeine, flunarizine, atenolol, and indomethacin also have been found to be effective in a number of patients with hypnic headache [22,23].

Diagnosis

Indomethacin-responsive headache disorders are clinically heterogeneous. However, they belong to a group of primary headache disorders in which individual headache episodes are characteristically short-lived. In contrast with migraine and tension-type headache, which usually last several hours (> 4 hours) to several days, this group of headache disorders last between seconds to 1 hour. Primary short-lasting headache disorders may be divided into those with and without cranial autonomic symptoms (Table 3). Because not every headache within this group is responsive to indomethacin, it is important to recognize the features that distinguish those that are responsive to indomethacin (Table 4). SUNCT syndrome is a relatively uncommon syndrome characterized by very brief (20–90 seconds), but frequent (average is 16, but up to 100 attacks daily) paroxysms of intense unilateral orbital/periorbital pain that usually is associated with robust lacrimation and conjunctival injection [24]. It is more common in men (2.3:1), with an average age of onset of 50 years. This syndrome, although very similar in its distribution and temporal profile to trigeminal neuralgia, can be distinguished by longer-lasting painful paroxysms, which are associated with robust ipsilateral autonomic symptoms. Indomethacin and medications characteristically effective for trigeminal neuralgia, migraine, and cluster headache generally are ineffective for SUNCT. However, carbamazepine may be effective in some patients [24]. Case reports of patients responding to lamotrigine and gabapentin also have been reported [25,26].

Practically, a trial of indomethacin should be considered for a patient with recurrent headaches of brief duration (< 1 hour), which are strictly unilateral, may occur several times daily, and may be associated with autonomic symptoms, precipitated by valsalva, exercise, or sexual activity, or awaken patients from sleep. The one exception, HC, although a persistent headache of long duration, can be recognized by its strict unilaterality, associated autonomic symptoms, and ice-pick pain. Even when these features appear to be absent, a patient with a long-standing continuous unilateral headache should receive a brief trial of indomethacin at a reasonable dosage (150 mg).

Treatment with Indomethacin

Indomethacin, the pharmacology of which is discussed in the next section, is the treatment of choice for the paroxysmal hemicranias and HC and has been considered the sine qua non for establishing the diagnosis. Treatment usually is initiated at a dose of 25 mg three times daily with meals. Treatment response is invariably swift once an appropriate dosage is attained. The average interval between drug ingestion and relief of pain in patients with HC and CPH is approximately 30 minutes and 48 hours, respectively [27]. Most patients report complete relief of headache within 24

hours and frequently within 8 hours. Interindividual differences in the dosage and timing needed to abolish the headaches exist and likely are secondary to differences in bioavailability and individual sensitivity. In patients who do not obtain relief within 48 hours of initiation, the dosage should be increased to 50 mg three times daily. Patients may obtain a partial response, but not complete relief from a suboptimal dosage. Treatment failure should be considered only if a patient has not responded to a dosage of 300 mg daily. Maintenance dosages between 25 and 100 mg usually are adequate in maintaining suppression of the headache. It is recommended that once an effective dosage is established for several weeks, the dosage should be reduced gradually in an effort to ascertain the lowest effective dosage. In a study involving 26 patients with HC or CPH who were followed for an average of 3.8 years, 42% experienced a mean decrease of 56% in the dose of indomethacin (41 mg ± 19 mg daily) required to maintain a pain-free state [28•].

Dosage adjustments sometimes are necessary to treat the clinical fluctuations that can be seen in these disorders. Because nocturnal attacks or exacerbations are seen frequently, a bedtime dosage of sustained-release indomethacin may be useful to prevent these attacks. Some patients are so exquisitely sensitive to indomethacin, even skipping one dose will allow the headache to recur. In patients with EPH, indomethacin usually is continued for approximately 2 weeks beyond the expected duration of the headache period. In patients with CPH and HC, although long-term indefinite treatment often is required, a periodic attempt to withdraw the medication is useful because long-term remissions have been described [10,27].

When patients are refractory to indomethacin therapy, the diagnosis should be reconsidered. However, typical cases of CPH and HC have been described as unresponsive to indomethacin [10,29]. Patients requiring a continuous high dosage of indomethacin and those patients who require increasing dosages after an initial response to a lower dosage may have underlying pathology and need careful evaluation [30]. Some patients with symptomatic CPH or HC as a result of intracranial or pulmonary lesions have been reported to respond to modest dosages of indomethacin [31–33], highlighting the need for a careful clinical assessment in patients who otherwise appear to have a typical clinical picture and response to medication.

Because the response of these headache disorders is swift, permanent, and often exclusive to indomethacin after many other medications have failed previously, some authorities argue that an absolute response to indomethacin should be considered a diagnostic requirement. To maintain the homogeneity of patient populations for research, the IHS has included a response to indomethacin as an obligatory criterion for the diagnosis of paroxysmal hemicrania and HC. However, from a clinical standpoint, although HC and CPH often respond in a dramatic manner to indomethacin, an obligatory response to indomethacin for diagnosis is problematic for a number of reasons. First, a therapeutic response in patients with HC is not exclusive to indomethacin or to nonsteroidal anti-inflammatory drugs (NSAIDs) in general. A variety of medications have been reported to be effective in patients with HC, including dihydroergotamine [34], methysergide [34], corticosteroids [35,36], acetaminophen with caffeine [37], lamotrigine [38], gabapentin [39], and lithium carbonate [40]. In addition, other NSAIDs including aspirin, naproxen, ibuprofen, diclofenac, rofecoxib, and piroxicam have been shown to have an absolute effect on some patients with HC, which met the diagnostic criteria proposed by Goadsby and Lipton [1] in 1997 [41,42]. Similarly, other medications have been found to be effective in patients with CPH, including acetylsalicylic acid [44], verapamil [44,45], corticosteroids [46], naproxen [43], a piroxicam derivative [47], and acetazolamide [48]. In light of this, patients with CPH and HC would not be diagnosed correctly in the event that a response to another medication occurred before a trial of indomethacin. Second, symptomatic HC and CPH have been described in patients who had an absolute response to indomethacin to the exclusion of numerous medications including opioids [10,31,32]. This nonspecific response underscores the potential peril in rendering a diagnosis based on the response to a medication. Although the response to a particular medication is used as a supportive (giant cell arteritis) or diagnostic (Tolosa-hunt syndrome) criterion for other headache types, these are secondary headache disorders that respond exclusively to corticosteroids. Third, other primary headache disorders, such as cough headache and idiopathic stabbing headache, also respond in a highly consistent manner to indomethacin. Therefore, a response to indomethacin is not specific to one particular headache disorder, nor is it specific to the TACs. Finally, patients presenting with a classical clinical phenotype of CPH and HC have been reported to be unresponsive to indomethacin [10,29]. In light of these issues, from the clinician's perspective, a response to indomethacin should not be considered necessary or sufficient to make a diagnosis of CPH, HC, or any primary headache disorder.

Indomethacin Pharmacology

Indomethacin is an indoleacetic acid derivative [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid] that is related structurally and pharmacologically to sulindac. Similar to other NSAIDs, indomethacin is a potent reversible inhibitor of prostaglandin-forming cyclooxygenase (COX). It also inhibits phosphodiesterase, thus enhancing intracellular cyclic adenosine monophosphate [49]. It was introduced in 1963 for the treatment of rheumatoid arthritis and related disorders because of its anti-inflammatory properties. Indomethacin is available in oral, rectal, and intravenous formulations, although the latter is approved for the treatment of patent ductus arteriosus in premature infants only. Although limited data exist regarding intravenous dosing in

adults, peak plasma concentrations usually are attained within 5 minutes [9]. Indomethacin is rapidly and almost completely absorbed from the gastrointestinal tract after oral ingestion, with peak plasma concentrations occurring within 30 to 120 minutes after ingestion. Oral bioavailability is nearly 100%. Absorption is more rapid with rectal than with oral administration, but peak plasma concentrations are lower and the bioavailability is approximately 80% compared with that of the intravenous dose.

Indomethacin is bound extensively (90%) to plasma proteins and tissues. It is converted primarily to inactive metabolites by *O*-demethylation (50%), glucuronidation (10%), and *N*-deacylation. Approximately 10% to 20% of the drug is excreted unchanged in the urine, in part by tubular secretion. The plasma half-life averages approximately 3 hours, but can be quite variable partly because of extensive enterohepatic cycling. Data on the penetration of indomethacin into the central nervous system are conflicting. An early study of three healthy volunteers indicated limited distribution in the CSF after 2 hours [50]; however, in a more recent study, the drug rapidly entered the CSF, with levels ranging from less than 1 ng/mL to 11.9 ng/mL [51].

More than 35% of patients receiving therapeutic dosages of indomethacin experience adverse effects and approximately 20% must discontinue taking the drug. Most adverse effects are dose-related, emphasizing the importance of achieving the lowest effective dose possible. The most frequent gastrointestinal complications include anorexia, nausea, vomiting, dyspepsia (3% to 9% of patients), abdominal pain, mucosal ulceration, and diarrhea (< 1% of patients). Although gastrointestinal side effects may occur in up to one third of patients with long-term treatment, they seldom appear to be a reason for discontinuation [10,28•]. Gastrointestinal side effects often can be managed with antacids, misoprostol, or histamine H2 antagonists. Acute pancreatitis and fatal liver involvement are rare, but have been reported. Indomethacin also can impair renal function by decreasing urine output, the glomerular filtration rate, and creatinine clearance. The mechanism appears to be inhibition of renal prostaglandins, which are important for maintaining renal vascular tone. The renal effects usually are transient and are more likely to occur in patients with pre-existing renal impairment. Central nervous system side effects include headache, dizziness and mental confusion, somnolence, and fatigue. Severe depression, psychosis, hallucinations, and suicide have been reported. Hematopoietic reactions, including neutropenia, thrombocytopenia, and, rarely, aplastic anemia can occur.

Indomethacin should not be used in conjunction with oral anticoagulants because of the increased risk of gastrointestinal tract and systemic bleeding. Indomethacin also antagonizes the natriuretic effects of furosemide and the antihypertensive effects of thiazide diuretics, β-blockers, and angiotensin-converting enzyme inhibitors.

The mechanism by which indomethacin exerts its effect on certain TACs is unclear. Because these disorders do not respond to other NSAIDs often, a mechanism of COX inhibition seems likely. Although indomethacin shows some preference for COX-1 over COX-2 inhibition, piroxicam and aspirin are equally potent COX-1 inhibitors and do not appear to have as robust a treatment effect on these headache disorders [52]. Indomethacin and aspirin are effective inhibitors of neurogenic inflammation, which is thought to be partly responsible for the maintenance of head pain during migraine and other primary neurovascular headache disorders [53]. Although an obvious site of action of NSAIDs is in the periphery (at sites of inflammation), recent work has confirmed that a site of the analgesic action of indomethacin and other COX inhibitors also is central, specifically at the level of the spinal dorsal horn [54,55]. Indomethacin also has been shown to inhibit the production of nitric oxide [56]. This latter mechanism also may be important in understanding its therapeutic effect in headache because there is a large body of evidence implicating nitric oxide in the pathogenesis of migraine and cluster headache [57,58]. With particular reference to the TACs, nitric oxide has been found to be co-localized with VIP within the neurons and nerve fibers of the cranial parasympathetic system [59,60]. Therefore, indomethacin may antagonize one or more steps in the nitric oxide pathway and, in this way, exert its effect on disorders that are characterized by activation of the cranial parasympathetic system.

The therapeutic effect of indomethacin on valsalva-induced headaches may result from a sustained decrease in ICP. Considerable evidence from basic and clinical studies indicates that indomethacin decreases ICP for patients in whom it is increased, particularly after head injury or in cases of acute liver failure [49,61,62]. The proposed mechanisms for this decrease in ICP include decreased cerebral blood flow, inhibition of cerebral edema, decreased cerebral temperature, and decreased CSF production. Preliminary clinical studies indicate that the decrease in ICP associated with indomethacin is more robust and sustained than that occurring with hyperventilation or after administration of mannitol or barbiturates [63]. The decrease in ICP may be the basis for the effectiveness of indomethacin in the valsalva-induced headache syndromes. The effect of a valsalva maneuver is an increase of approximately 40 mmHg in intrathoracic and intra-abdominal pressure, which impedes venous return to the right atrium and, thus, increases central venous pressure. Because the epidural venous plexus and jugular venous system do not have valves, intracranial venous pressure is increased, with an immediate rise in dependent ICP. These sudden short-lasting headaches may be provoked by a sudden increase in ICP, which remits gradually over a short period of time. The report of complete resolution of cough headache in six patients after lumbar puncture was presumably mediated by a decrement in ICP [8].

Conclusions

An understanding of the mechanism by which indomethacin exerts its effect on this heterogenous group of primary head-

ache disorders will undoubtedly enhance our understanding of the underlying pathogenesis of these disorders. Ultimately, an improved understanding of the mechanism of these headaches will enable the development of safer and better tolerated therapies.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Goadsby PJ, Lipton RB: **A review of paroxysmal hemicranias, SUNCT syndrome and other short-lasting headaches with autonomic features, including new cases.** *Brain* 1997, 120:193–209.
2. Goadsby PJ, Edvinsson L: **The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats.** *Ann Neurol* 1993, 33:48–56.
3. Goadsby PJ, Edvinsson L: **Human in vivo evidence for trigeminovascular activation in cluster headache: neuropeptide changes and effects of acute attacks therapies.** *Brain* 1994, 117:427–434.
4. Goadsby PJ, Edvinsson L: **Neuropeptide changes in a case of chronic paroxysmal hemicrania: evidence for trigeminoparasympathetic activation.** *Cephalalgia* 1996, 16:448–450.
5. May A, Bahra A, Buchel C, *et al.*: **Hypothalamic activation in cluster headache attacks.** *Lancet* 1998, 352:275–278.
6. May A, Bahra A, Buchel C, *et al.*: **Functional magnetic resonance imaging in spontaneous attacks of SUNCT: short-lasting neuralgiform headache with conjunctival injection and tearing.** *Ann Neurol* 1999, 46:787–790.
7. Pascual J, Iglesias F, Oterino A, *et al.*: **Cough, exertional, and sexual headaches: an analysis of 72 benign and symptomatic cases.** *Neurology* 1996, 46:1520–1524.
8. Raskin NH: **The cough headache syndrome: treatment.** *Neurology* 1995, 45:1784.
9. Antonacci F, Sjaastad O: **Chronic paroxysmal hemicrania (CPH): a review of the clinical manifestations.** *Headache* 1989, 29:648–656.
10. Boes C, Dodick DW: **The clinical spectrum of chronic paroxysmal hemicrania seen at the Mayo Clinic from 1976–1996.** *Headache* 2003, in press.
11. Russell D: **Chronic paroxysmal hemicrania: severity, duration, and time of occurrence of attacks.** *Cephalalgia* 1984, 4:53–56.
12. Manzoni GC, Terzano MG, Bono G, *et al.*: **Cluster headache: clinical findings in 180 patients.** *Cephalalgia* 1983, 3:21–30.
13. Newman LC, Lipton RB, Soloman S: **Hemicrania continua: ten new cases and a review of the literature.** *Neurology* 1994, 44:2111–2114.
14. •• Peres MF, Silberstein SD, Nahmias S, *et.al.*: **Hemicrania continua is not that rare: 26 new cases.** *Neurology* 2001 7:948–951.

Very informative.

15. Perez MF, Siow HC, Rozen TD: **Hemicrania continua with aura.** *Neurology* 2001, 56(suppl 3):A452.
16. Bordini C, Antonaci F, Stovner LJ, *et al.*: **Hemicrania continua: a clinical review.** *Headache* 1991, 31:20–26.
17. Rooke ED: **Benign exertional headache.** *Med Clin North Am* 1968, 52:801–808.
18. Rasmussen BK, Jensen R, Schroll M, *et al.*: **Epidemiology of headache in a general population: a prevalence study.** *J Clin Epidemiol* 1991, 44:1147–1157.
19. Headache Classification Committee of the International Headache Society: **Classification and Diagnostic Criteria for headache disorders, cranial neuralgias, and facial pain.** *Cephalalgia* 1988, 8:1–96.
20. Pareja JA, Ruiz J, de Isla C, *et al.*: **Idiopathic stabbing headache.** *Cephalalgia* 1996, 16:93–96.
21. Raskin NL: **The hypnic headache syndrome.** *Headache* 1988, 28:534–536.
22. Dodick DW, Mosek A, Campbell JK: **The hypnic ("alarm clock") headache syndrome.** *Cephalalgia* 1998, 18:152–156.
23. Dodick DW: **Hypnic headache: another indomethacin-responsive headache syndrome?** *Headache* 2000, 40:830–835.
24. Pareja JA, Sjaastad O: **SUNCT syndrome: a clinical review.** *Headache* 1997, 37:195–202.
25. D'Andrea G, Granella F, Cadaldini M: **Possible usefulness of lamotrigine in the treatment of SUNCT syndrome.** *Neurology* 1999, 53:1609.
26. Graff-Radford SB: **SUNCT syndrome responsive to gabapentin (Neurontin).** *Cephalalgia* 2000, 20:515–517.
27. Pareja JA, Sjaastad O: **Chronic paroxysmal hemicrania and hemicrania continua: interval between indomethacin administration and response.** *Headache* 1996, 36:20–23.
28. • Sanchez del Rio M, Caminero AB, Pascual J, *et al.*: **Dose and efficacy of long-term indomethacin treatment of chronic paroxysmal hemicrania and hemicrania continua.** *Cephalalgia* 2001, 21:507.

Important study.

29. Kuritzky A: **Indomethacin-resistant hemicrania continua.** *Cephalalgia* 1992, 12:57–59.
30. Sjaastad O, Stovner LJ, Stolt-Nielsen A, *et al.*: **CPH and hemicrania continua: requirements of high indomethacin dosages. An ominous sign?** *Headache* 1995, 35:363–367.
31. Eross EJ, Swanson JW: **Hemicrania continua: an indomethacin-responsive case with an underlying malignant etiology.** *Neurology* 2001, 56(suppl 3):A452.
32. Antonaci F, Sjaastad O: **Hemicrania continua: a possible symptomatic case, due to mesenchymal tumor.** *Funct Neurol* 1992, 7:471–474.
33. Sjaastad O, Antonaci F: **Chronic paroxysmal hemicrania and hemicrania continua: transition from one stage to another.** *Headache* 1993, 33:551–554.
34. Young WB, Silberstein SD: **Hemicrania continua and symptomatic medication overuse.** *Headache* 1993, 33:485–487.
35. Newman LC, Lipton RB, Soloman S: **Hemicrania continua: ten new cases and a review of the literature.** *Neurology* 1994, 44:2111–2114.
36. Pascual J: **Hemicrania continua.** *Neurology* 1995, 45:2302–2303.
37. Bordini C, Antonaci F, Stovner LJ, *et al.*: **Hemicrania continua: a clinical review.** *Headache* 1991, 31:20–26.
38. Wheeler SD: **Lamotrigine efficacy in migraine prevention.** *Cephalalgia* 2001, 21:368–383.
39. Mariano HS, Alcantara MC, Bordini CA, Speciali JG: **Relief of continuous hemicrania by gabapentin: a case report.** *Cephalalgia* 2001, 21:504–509.
40. Joubert J: **Hemicrania Continua in a black patient: the importance of the non-continuous stage.** *Headache* 1991, 31:482–484.
41. Wheeler SD: **Rofecoxib-responsive hemicrania continua.** *Headache* 2000, 40:436–437.
42. Trucco M, Antonaci F, Sandrini G: **Hemicrania continua: a case responsive to piroxicam-beta-cyclodextrin.** *Headache* 1992, 32:39–40.
43. Antonaci F, Sjaastad O: **Chronic paroxysmal hemicrania (CPH): a review of the clinical manifestations.** *Headache* 1989, 29:648–656.
44. Coria F, Claveria LE, Jimenez-Jimenez FJ, de Seijas EV: **Episodic paroxysmal hemicrania responsive to calcium channel blockers.** *J Neurol Neurosurg Psychiatry* 1992, 55:166.
45. Shabbir N, McAbee G: **Adolescent chronic paroxysmal hemicrania responsive to verapamil monotherapy.** *Headache* 1994, 34:209–210.
46. Hannerz J, Ericson K, Bergstrand G: **Chronic paroxysmal hemicrania: orbital phlebography and steroid treatment.** *Headache* 1987, 7:189–192.

47. Sjaastad O, Antonaci F: **A Piroxicam derivative partially effective in chronic paroxysmal hemicrania and hemicrania continua.** *Headache* 1995, 35:549–550.
48. Warner JS, Wanul AW, McLean MJ: **Acetazolamide for the treatment of chronic paroxysmal hemicrania.** *Headache* 1994, 34:597–599.
49. Harrigan MR, Tuteja S, Neudeck BL: **Indomethacin in the management of elevated intracranial pressure: a review.** *J Neurotrauma* 1997, 14:637–650.
50. Rothermich NO: **The fate of rectally administered radioactive indomethacin in humnan subjects.** *Clin Pharmacol Ther* 1971, 12:300–301.
51. Bannwarth B, Netter P, Lapicque F, *et al.*: **Plasma and cerebrospinal fluid concentrations of indomethacin in human.** *Euro J Clin Pharmacol* 1990, 38:343–346.
52. Frolich JC: **A classification of NSAIDs according to the relative inhibition of cyclooxygenase isoenymes.** *Trends Pharmacol Sci* 1997, 18:30–34.
53. Dimitriadou V, Buzzi MG, Theoharides TC, Moskowitz MA: **Ultrastructural evidence for neurogenically mediated changes in blood vessels of the rat dura mater and tongue following antidromic trigeminal stimulation.** *Neuroscience* 1992, 48:187–203.
54. Pitcher GM, Henry JL: **Mediation and modulation by eicosanoids of responses of spinal dorsal horn neurons to glutamate and substance P receptor agonists: results with indomethacin in the rat in vivo.** *Neuroscience* 1999, 93:1109–1121.
55. Pitcher GM, Henry JL: **NSAID-induced cyclooxygenase inhibition differentially depresses long-lasting versus brief synaptically elicited responses of rat spinal dorsal horn neurons in vivo.** *Pain* 1999, 82:173–186.
56. Du ZY, Li XY: **Inhibitory effects of indomethacin on interleukin-1 and nitric oxide production in rat microglia in vitro.** *Int J Immunopharmacol* 1999, 21:219–225.
57. Thomsen LL, Olesen J: **Nitric oxide theory of migraine.** *Clin Neurosci* 1998, 1:28–33.
58. Lassen LH, Ashina M, Christiansen I, *et al.*: **Nitric oxide synthase inhibition: a new principle in the treatment of migraine attacks.** *Cephalalgia* 1998, 18:27–32.
59. Goadsby PJ, Uddman R, Edvinsson L: **Cerebral vasodilation in the cat involves nitric oxide from parasympathetic nerves.** *Brain Res* 1996, 707:110–118.
60. Uddman R, Tajti J, Moller S, *et al.*: **Neuronal messenger molecules and peptide receptors distribution in the human cranial parasympathetic ganglia.** *Cephalalgia* 1999, 19:392.
61. Clemmesen JO, Hansen BA, Larsen FS: **Indomethacin normalizes intracranial pressure in acute liver failure: a 23-year-old woman treated with indomethacin.** *Hepatology* 1997, 26:1423–1425.
62. Jensen K, Öhrström J, Cold GE, Astrup J: **The effects of indomethacin on intracranial pressure, cerebral blood flow, and cerebral metabolism in patients with severe head injury and intracranial hypertension.** *Acta Neurochir (Wien)* 1991, 108:116–121.
63. Biestro AA, Alberti RA, Soca AE, *et al.*: **Use of indomethacin in brain-injured patients with cerebral perfusion pressure impairment: preliminary report.** *J Neurosurg* 1995, 83:627–630.

EXHIBIT B

CLASSIFICATION OF CHRONIC PAIN

DESCRIPTIONS OF CHRONIC PAIN SYNDROMES AND DEFINITIONS OF PAIN TERMS

Second Edition

prepared by the

Task Force on Taxonomy
of the
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GROUP V: PRIMARY HEADACHE SYNDROMES, VASCULAR DISORDERS, AND CEREBROSPINAL FLUID SYNDROMES

Classic Migraine (Migraine with Aura) (V-1)

Definition
Throbbing head pain in attacks, often with a prodromal state and usually preceded by an aura which frequently contains visual phenomena. The pain is typically unilateral but may be bilateral. Nausea, vomiting, photophobia, and phonophobia often accompany the pain. Clear female predominance.

Site
Typically unilateral, but may be bilateral. Pain mostly begins in the fronto-temporal area and is most marked in this area, even at maximum, when it may involve the whole hemicranium. The side typically changes in different attacks or even during single attacks.

System
Unknown: vascular disturbances have been emphasized; central nervous system changes may be fundamental. The coding below accepts the latter.

Main Features
Frequent positive family history of migraine-like type of headache. *Prevalence:* high, but less frequent than common migraine. *Sex Ratio:* females more than males. *Onset:* from childhood to about 35. In most cases, attacks have started by late puberty. Onset of solitary attacks may be associated with emotional stress, relaxation, "anxiety," dietary causes (chocolate, cheese, citrus fruits, etc.), flashing lights, atmospheric changes, etc. *"Premonitory" Phase:* may last for hours to one or two days and precedes the aura phase, often with mood changes, weight gain. *The Aura* usually precedes the pain phase but may also occur both prior to and during it, and occasionally only during it. An aura may occur without subsequent pain, probably most frequently in male patients. In approximate order of frequency, the following phenomena occur during the aura phase: blurring of vision, flickering changes in the visual field, phenomena like a curtain or mist in parts of the field, fortification figures, scotomata and a variety of other visual changes (the visual changes usually have a homonymous distribution), paresthesias, mostly in the regions of the hand and mouth, mild paresis (the two last phenomena usually with a unilateral distribution), dysarthria, and aphasic disturbances. In extremely rare cases, there may be alloesthesia, micropsia, and macropsia, or distortions of perspective. If paresis, hemianopias, and sensory loss are prominent and longlasting, they may be part of other migraine variants (V-3). *Duration of Aura Phase:* usually 20–25 minutes. *Pain:* the aura may overlap with the pain phase. Usually the pain succeeds the aura with or without a symptom-free interval. In occasional attacks in the classic migraineur, the pain starts without a preceding aura. The pain is throbbing, ranges from mild to severe in intensity, reaches a plateau, and usually lasts from 4 to 72 hours if unmodified by drugs. The pain may be global, but typically it is unilateral and alternates sides during an attack or between attacks. The pain typically starts in the frontal-temporal area. It may continue in that area or involve the entire hemicranium at a later stage. The pain is generally moderate to severe. Characteristically, the pulsating quality increases with moderate physical activity or stooping. *Frequency:* varies from a couple of attacks in a lifetime to several every week. The most usual pattern in clinical practice is 1–4 per month. Exacerbations often occur during episodes of anxiety, depressive illness, or personal conflict. The tendency to attacks is frequently markedly reduced in pregnancy. *Other Characteristics:* anorexia, nausea and vomiting, photophobia, and phonophobia are characteristic features of the attack.

Precipitating Factors
Numerous, may include stress, mood changes, relaxation, dietary factors.

Associated Symptoms and Signs
Anorexia, nausea, vomiting, photophobia, and phonophobia. With "complicated migraine," various deficiency symptoms and signs (e.g., hemiplegic migraine; see V-3).

Laboratory Findings
Fall in platelet serotonin during attacks. Changes in cerebral blood flow.

Relief
From ergot preparations, beta-blocking agents, calcium blocking agents, NSAIDs, and substances interfering with serotonin activity, in particular serotonin 1D receptor agonists like sumatriptan.

Usual Course
In time, interparoxysmal psychological changes if the headache is severe. Ergotamine dependence or other dependence on medication, even analgesic medication. Detoxification may be required to end a vicious circle of withdrawal headaches and medications.

Complications
Depression and related psychological changes if severe. Dependence on ergotamine or other medication.